PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 20 April 2001 (20.04.01)	
International application No. PCT/EP99/06369	**Applicant's or agent's file reference** P507PCT
International filing date (day/month/year) 30 August 1999 (30.08.99)	**Priority date** (day/month/year)
Applicant ROBINSON, John, A. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

09 March 2001 (09.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
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PATENT COOPERATION TREATY

REC'D 27 NOV 2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P507PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/06369	30/08/1999	30/08/1999
International Patent Classification (IPC) or national classification and IPC		
C07K7/02		
Applicant		
POLYPHOR AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/03/2001	23.11.2001
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Vogt, T Telephone No. +49 89 2399 8477

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/06369

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-72 as originally filed

Claims, No.:

1-9 as received on 08/10/2001 with letter of 05/10/2001

Drawings, sheets:

1/1 as originally filed

Sequence listing part of the description, pages:

1-17, filed with the letter of 05.01.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
   see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations
   see separate sheet

I Amendments (Art. 41 PCT).

The applicant filed a new set of claims 1-9 with the letter of 05.10.2001.

Amended claim 1 corresponds to claim 1 with the following amendments:

p. 2, l. 8-10 added: 'which process is ... and defined purities': to illustrate that the process is useful for parallel array synthesis (cf. p. 4, 7 and 15). It is noted that the fact that a process is 'useful for ...' does not imply that it cannot be used for something else, in this case the preparation of single compounds.

point (a) added: 'derived from polystyrene ... a 2-chlorotrityl linker': this restriction should be seen in combination with the above (cf. original claim 2, p. 15).

point (n) added: 'by means of ... ("HOAt")' (cf. p. 17-18).

Amended claims 2 and 3 are claims 5 and 6 as originally filed. Amended claims 4-6 relate to the process of claim 1 in a parallel array synthesis to yield a library of compounds (cf. p. 4, p. 16). Amended claims 7-9 relate to the library obtainable by the process of claim 4 (cf. p. 4, p. 16).

The invention as originally filed was directed to the position of the planar group inducing the β-turn motif during the peptide synthesis (cf. claim 1a as originally filed). This concept was already disclosed by the inventors in documents D1 and D7. With the amended set of claims the applicant tries to redefine the invention in terms of the solid support and the linker to be used in parallel array synthesis.

In the letter of reply the applicant states the restriction to solid supports derived from polystyrene cross linked with divinylbenzene renders the process applicable for parallel combinatorial chemistry, according to the inventors the solid support Tentagel is not suitable for this purpose. This statement clearly contradicts to the teaching of the description as originally filed (cf. p. 15, l. 23-31), and is therefore considered to be a new teaching.

In the letter of reply the applicant also states that the use of a Sasrin functionalised support is unfavourable for use in automated processes, whereas the use of a 2-chlorotrityl linker allows recovery under mild conditions, thereby resulting in less side reactions. The description (p. 16, l. 9-24) lists various linkers as alternatives, nowhere can it be found in the description that one or more linkers are more suitable then others for the process of parallel array synthesis. Hence, this is considered to be a new

teaching not found in the application as originally filed.

The applicant states that in all peptide synthesis examples only solid supports derived from polystyrene cross linked with divinylbenzene are used functionalised with 2-chlorotrityl. The examiner acknowledges that 2-chlorotrityl functionalised solid supports are used, but could not find any support for the use of solid supports derived from polystyrene cross linked with divinylbenzene.

Hence, it appears that the applicant made a novel selection from several alternatives to overcome the novelty objections and to focus on a process for the preparation of a library of cyclic peptides. The amendments therefore contravene with Art. 41 PCT.

Nevertheless, the examiner will continue the substantive examination.

V Reasoned Statement (Rule 66(2) PCT).

Subject matter of the present application.

The provision of a process for the preparation of compounds of general formula 1.

Cited prior art documents (Rule 64(1) PCT).

D1: Favre et al. (03.1999) J. Am. Chem. Soc. 121, 2679-2685.
D2: Sato et al. (1991) Int. J. Peptide Protein Res. 38, 340-345.
D3: Pfeifer & Robinson (1998) Chem. Commun., 1977-1978.
D4: Späth et al. (1998) Helv. Chim. Acta 81, 1726-1738.
D5: Obrecht et al. (04.1999) Adv. Med. Chem. 4, 1-68.
D6: Hanessian et al. (1997) Tetrahedron 53, 12789-12854.
D7: EP-A-0592791.
D8: US-A-5670155.

Novelty (Art. 33(2) PCT).

D1 discloses the preparation of cyclic β-Turn peptide mimetics containing a D-Pro-Pro template. The method of preparation is identical to that of claim 1 of the present application for the D-Pro-Pro template A (cf. Experimental section). The template is bound approximately in the middle of the linear peptide, whereafter the peptide is

detached from the Tentagel-S AC solid support (Sasrin modified solid support derived from polystyrene cross linked with PEG spacers) and cyclised with HATU, HOAt and DIEA. The amendment in claim 1(a) that the solid support must be derived from polystyrene cross linked with divinylbenzene and functionalised with a 2-chlorotrityl linker renders amended claim 1 novel over D1.

D2 discloses the use of BTD to incorporate into a peptide a motif that corresponds to a β-Turn. Although the strategy followed by D2 is similar to that of the present application, D2 does not cyclise its peptides as a last synthesis step.

D3 relates to β-hairpin conformations in cyclic peptides using a bicyclic template (compound 3=template c of claim 1). The synthesis of the cyclic peptides of D3 differs from the present application in that the template is added as the first 'AA' to the solid support not in the middle as suggested by the present application.

D4 relates to β-hairpin conformations in cyclic peptides using a D-Pro-Pro template. The synthesis of the cyclic peptides of D4 differs from that of the present application (and D1) in that the template is added as the last 'AA'.

D5 is a review written by the inventors of the present application. It discloses amongst others several different templates for use in cyclic peptide mimetics with β-hairpin conformations (see Figs 20 and 21), and the preparation of libraries comprising structurally constrained peptides.

D6 discloses some other templates for use in the design of conformationally restricted cyclic peptides. (see Chapter IX, for an extensive list of templates).

D7 is referred to in the description as being the closest prior art (cf. p. 7). It discloses the templates f, g and h of claim 1 and the use thereof for the preparation of conformationally restricted cyclic peptides. D7 discloses various strategies to obtain cyclic peptides one of which falls within the scope of claim 1. In example 1.5.3 D7 discloses the synthesis of the cyclic peptide 4,5-cyclo[-acetyl-Val-Arg-Lys-Ile-aminomethyl]-3,6-dimethoxy-9,9-dimethylxanthen-trifluoroacetate starting from FMOC-Lys-Sasrin functionalised resin derived from polystyrene cross linked with divinyl benzene. In accordance with D1, the amendment that the solid support must be derived

from polystyrene cross linked with divinylbenzene functionalised with a 2-chlorotrityl linker (not Sasrin) and the fact that the cyclisation must be performed with HATU/HOAt (not HBTU) renders the subject matter of claim 1 novel over D7.

Inventive step (Art. 33(3) PCT).
As indicated above present claim 1 differs only from the teaching of D7 (example 1.5.3) in the solid linker and the chemicals used for the cyclisation. The chemicals (HATU/HOAt) used for the cyclisation in the present application are disclosed in D1.

At present the examiner is of the opinion that the differences of present claim 1 with D1 and D7 are merely known alternatives.

In the letter of reply the applicant stresses the importance of peptide libraries and in particular libraries of structurally constrained peptides. The IPEA acknowledges the importance of such libraries, however, such libraries are already known in the art. In addition the importance of structurally constrained β-turn peptides as ligands was already disclosed (cf. D1, D5 and D7). Hence, it would have been an obvious next step for a skilled artisan to prepare libraries of such structurally constrained β-turn peptides.

When a skilled artisan is faced with the problem of adapting the process of D1 and D7 for use in a parallel array synthesis, he would choose a solid support suitable for and based on, the strategy to be used (cf. Tetrahedron Organic Chemistry Series Vol. 17, cited in the description). Also the substitution of a one linker for another is considered to be standard process optimization in solid-phase peptide synthesis and is mainly determined by the nature of the peptide(s) to be synthesized.

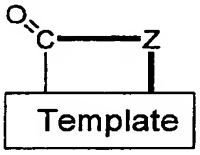
Furthermore, the applicant has not provided any experimental evidence showing an unexpected positive effect.

Hence, the examiner is of the opinion that the subject matter of the present application lacks an inventive step over the combined teaching of D1, D5, and D7.

Industrial applicability (Art. 33(4) PCT).
The process of the present application can be used to synthesize structurally restrained peptides.

CLAIMS

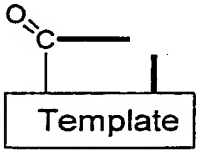
1. A process for the manufacture of compounds of the general formula



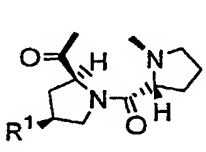
I

wherein

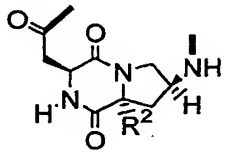
Z is a chain of n α-amino acid residues which, if their α-C atom is asymmetric, have L-configuration, n being an integer from 4 to 20, the positions of said amino acid residues in said chain being counted starting from the N-terminal amino acid;



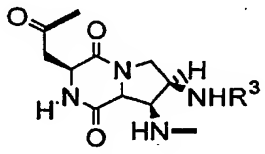
is one of the groups of formulae



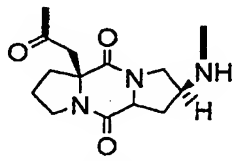
(a)



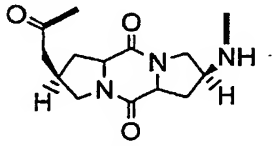
(b)



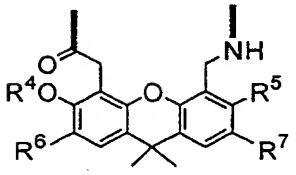
(c)



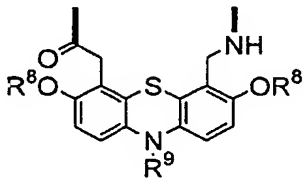
(d)



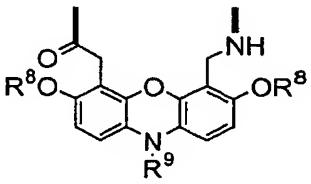
(e)



(f)



(g)



(h)

R^1 is hydrogen or a protected amino group;

R^2 is hydrogen or a group of formula CH_2-$COOR^{10}$;

R^3 is an amino-protecting group;

R^4 is lower alkyl or aryl-lower alkyl;

R^5 is lower alkyl, lower alkoxy or aryl;

R^6 is hydrogen, lower alkyl, substituted lower alkyl, aryl, Br or NO_2;

R^7 is hydrogen, lower alkyl, substituted lower alkyl, aryl, Br or NO_2;

R^8 is lower alkyl, substituted lower alkyl or aryl-lower alkyl;

R^9 is lower alkyl, substituted lower alkyl or aryl-lower alkyl; and

R^{10} is hydrogen, lower alkyl, substituted lower alkyl, aryl, aryl-lower alkyl, aroyl-lower alkyl or allyl;

and of salts thereof, which process is capable of being carried out as parallel array synthesis to yield libraries of numerous compounds of formula I in high yields and defined purities and which comprises

(a) coupling a solid support derived from polystyrene crosslinked with divinylbenzene which is functionalized by means of a 2-chlorotrityl linker with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position $^n/_2$, $^n/_2+1$ or $^n/_2-1$ if n is an even number and, respectively, in position $^n/_2+^1/_2$ or $^n/_2-^1/_2$ if n is an odd number, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

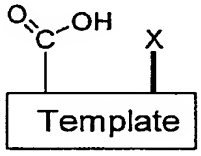
(b) removing the N-protecting group from the product thus obtained;

(c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position nearer the N-terminal amino acid residue, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(d) removing the N-protecting group from the product thus obtained;

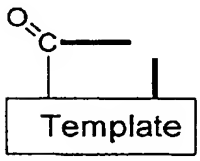
(e) repeating, if necessary, steps (c) and (d) until the N-terminal amino acid residue has been introduced;

(f) coupling the product thus obtained with a compound of the general formula

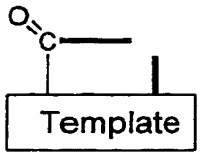


II

wherein

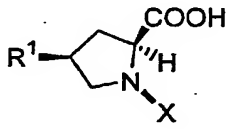


is as defined above and X is an N-protecting group or, if



is to be group (a), above, alternatively

(fa) coupling the product obtained in step (d) or (e) with a compound of the general formula **III**



III

wherein R^1 and X are as defined above;

(fb) removing the N-protecting group from the product thus obtained; and

(fc) coupling the product thus obtained with an appropriately N-protected derivative of D-proline;

(g) removing the N-protecting group from the product obtained in step (f) or (fc);

(h) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position n, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(i) removing the N-protecting group from the product thus obtained;

(j) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position farther away from position n, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(k) removing the N-protecting group from the product thus obtained;

(l) repeating, if necessary, steps (j) and (k) until all amino acid residues have been introduced;

(m) detaching the product thus obtained from the solid support;

(n) cyclising the product cleaved from the solid support by means of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate ("HATU") / 7-aza-1-hydroxybenzotriazole ("HOAt");

(o) removing any protecting groups present on functional groups of any members of the chain of amino acid residues and, if desired, any protecting group(s) which may in addition be present in the molecule; and

(p) if desired, converting the product thus obtained into a salt or converting a salt thus obtained into the corresponding free compound of formula I or into a different salt.

2. A process according to claim 1 wherein X and the N-protecting group of the amino acid derivatives is 9-fluorenylmethoxycarbonyl (Fmoc).

3. A modification of the process according to claim 1 or 2 for the manufacture of enantiomers of the compounds of formula I as defined in claim 1 in which all amino acids which have an asymmetric α-carbon atom are used in their D-Form and the enantiomer of a template corresponding to structure (a), (b), (c), (d) or (e) or a template corresponding to formula (f), (g) or (h) is used in step (f) and, respectively, the enantiomer of a compound of formula III is used in step (fa) and a derivative of L-proline is used in step (fc).

4. A process according to any one of claims 1 to 3 which is carried out as parallel array synthesis to yield a library of numerous compounds of formula I as defined in claim 1 or enantiomers thereof.

5. A process according to claim 4 wherein the library comprises 24 to 192 compounds.

6. A process according to claim 5 wherein the library comprises 96 compounds.

7. A library of numerous compounds of the general formula I as defined in Claim 1 or enantiomers thereof, obtainable by the process according to claim 4.

8. A library according to claim 7 comprising 24 to 192 compounds, obtainable by the process according to claim 5.

9. A library according to claim 8 comprising 96 compounds, obtainable by the process according to claim 6.